Cancer Chemother Pharmacol (2007) 59: 149–150
DOI 10.1007/s00280-006-0243-4

LETTER TO THE EDITOR

Camillo Porta · Luciano Mutti · Gianfranco Tassi

Negative results of an Italian Group for Mesothelioma (G.I.Me.) pilot study of single-agent imatinib mesylate in malignant pleural mesothelioma

Received: 18 February 2006 / Accepted: 24 March 2006 / Published online: 25 April 2006

Sir,

Platelet-derived growth factor receptor (PDGFR) and C-kit are two tyrosine kinase receptors that have been implicated in several malignancies, including malignant mesothelioma (MMe).

Indeed, overexpression of PDGF-β receptors has been demonstrated in MMe cell lines, xenografts as well as in patient specimens. Furthermore, one of the most common genetic abnormalities observed in MMe involves chromosome 22q13, which codes for the β-chain of PDGF; finally, blocking either PDGFR-β or PDGFR-α resulted in MMe growth inhibition [1].

Regarding C-kit, despite a large amount of uncertainty concerning the entity, type, and even the presence, of its expression in MMe [2], transfection of C-kit in MMe cells, in the presence of its ligand stem cell factor (SCF), up-regulates the transcriptional repressor Slug and increases the resistance to several chemotherapeutic agents [3].

We thus performed a pilot study of single-agent imatinib mesylate (Gleevec™), a tyrosine kinase inhibitor that targets both PDGF-R and C-kit, in naïve as well as pre-treated MMe patients.

Eligibility criteria included: histologically proven, PDGFR-β and/or C-kit-positive, unresectable or recurring MMe, measurable disease, an ECOG Performance Status of ≤ 2, a CALGB prognostic score of ≤ 4, age ≥ 18 and < 70 years, at least 12 weeks' life expectancy, as well as a written informed consent; patients were also required to have adequate organ function.

Gleevec™, directly purchased by G.I.Me., was given, per os, at the dose of 200 mg b.i.d.; disease status was evaluated at baseline and then every 2 months on spiral high-resolution CT images using the recently developed and validated modified RECIST criteria for MMe.

Treatment-related toxic effects were recorded and reported according to the NCI-CTC version 3.0.

Eleven patients were enrolled in this pilot study, whose characteristics are reported in Table 1.

No objective responses were observed, the best result obtained being disease stabilization in four patients only (36.3%); the remaining seven patients (63.6%) progressed, despite treatment.

Median time to progression (TTP) was 8 weeks (average 10.9 ± 4.39, range 7–19), while median overall survival was 20 weeks (average 22.09 ± 11.16, range 9–42), fairly better for those who obtained a disease stabilization (average 29.5 vs. 14 weeks).

Treatment was well tolerated, with few cases of grade 3/4 toxicities (nausea 2/11, i.e., 18.1%; neutropenia, fatigue, edema and rash 1/11, i.e., 9% each).

Malignant mesothelioma is relatively resistant to chemotherapy and, until the recent registration of Pemetrexed, no regimen has emerged as a standard of care.

Even though a real breakthrough, these results should still be considered as unsatisfactory; thus, MMe is still an ideal field to test new therapeutic strategies, including molecularly targeted treatments.

In accordance with two previous experiences [4], [5], we demonstrated no activity of single-agent Gleevec in MMe patients. However, recent data from our laboratory suggest that Gleevec could synergize with some chemotherapeutic agents, at least in vitro [6]. Thus, despite the above results, the inhibition of the PDGFR and C-kit pathways deserves further studies in MMe.

C. Porta (✉)
Medical Oncology, I.R.C.C.S. San Matteo University Hospital,
Piazzale C. Golgi, 27100 Pavia, Italy
E-mail: c.porta@smatteo.pv.it
Tel.: +39-0382-501355
Fax: +39-0382-526223

L. Mutti
Local Health Authority 11, Piedmont, Italy

G. Tassi
Pneumology, Civic Hospital, Brescia, Italy

Table 1 Patients' characteristics

Patients	
Males	8 (72.20%)
Females	3 (27.20%)
Age (years)	
Average	58.63
Median	59
Range	42–71
Histology	
Epithelioid	8 (72.20%)
Biphasic	3 (27.20%)
Sarcomatoid	0
Receptor status at immunohistochemistry	
PDGFR +	5 (45.40%)
C-kit +	6 (54.50%)
PDGFR and C-kit +	4 (36.30%)
ECOG Performance Status	
0	0
1	4 (36.30%)
2	7 (63.60%)
CALGB score	
1	0
2	3 (27.20%)
3	7 (63.60%)
4	1 (9.00%)
Sites of disease	
Chest only	6 (54.50%)
Chest and extra-thoracic	5 (45.40%)
Previous treatments	
Therapy-naïve	2 (22.20%)
$\geq$ 1 previous line	9 (81.80%)

References

1. Vogelzang NJ, Porta C, Mutti L (2005) New agents in the management of malignant mesothelioma. Semin Oncol 32:336–350
2. Butnor KJ, Burchette JL, Sporn TA, Hammar SP, Roggli VL (2004) The spectrum of Kit (CD117) immunoreactivity in lung and pleural tumors: a study of 96 cases using single-source antibody with a review of the literature Arch Pathol Lab Med 128:538–543
3. Catalano A, Rodilossi S, Rippo MR, Caprari P, Procopio A (2004) Induction of stem cell factor/C-kit/slug signal transduction in multidrug-resistant malignant mesothelioma cells J Biol Chem 279:46706–46714
4. Villano JL, Husain AN, Stadler WM, Hanson LL, Vogelzang NJ, Kindler HL (2004) A phase II trial of imatinib mesylate in patients (pts) with malignant mesothelioma (MM). Abs Am Assoc Clin Oncol 23:663 (abs. 7200)
5. Mathy A, Baas P, Dalesio O, van Zandwijk N (2005) Limited efficacy of imatinib mesylate in malignant mesothelioma: a phase II trial Lung Cancer 50:83–86
6. Cacciotti P, Barbone D, Porta C, Mutti L, Gaudino G (2004) STI571 and gemcitabine combined cell treatment as a novel approach to malignant mesothelioma therapy. Abs. VII meeting of the International Mesothelioma Interest Group (IMIG), p 99